2025
12(2), 1266

Chemical Biology
LETTERS

Impact of MYC on metabolic reprogramming, cellular energetics, and tumorigenesis in Breast cancer

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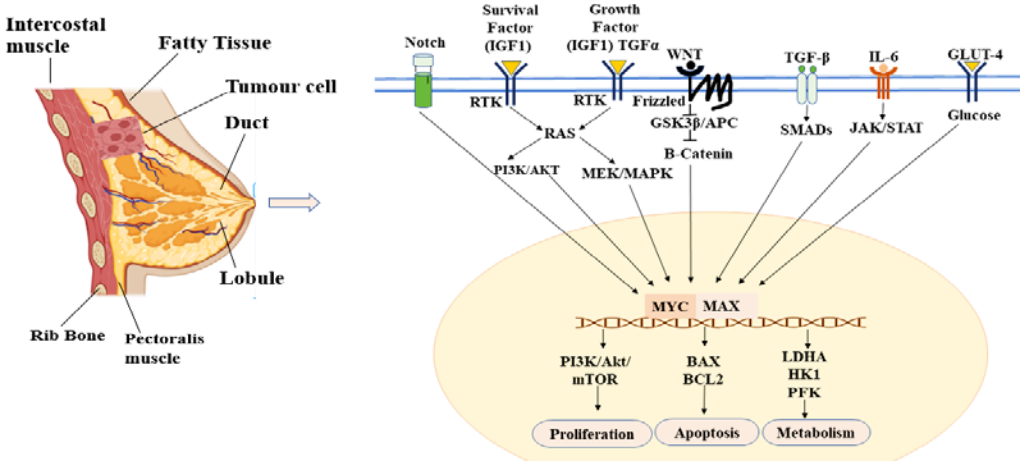
Submitted on: 11-Dec-2024, Accepted and Published on: 04-Mar-2025

Article

ABSTRACT



Breast cancer is the most fatal malignancy reported in females. About 1.38 million cases of breast cancer were reported in 2022 among which 50% of breast cancer patients and around deaths of 60% had occurred in developing countries. A kind of transcription factor called MYC, encoded by the MYC oncogene, has a wide range of actions and an unexplained carcinogenic role. According to the available data, MYC initiates a gene amplification process through gene expression that fosters cell proliferation growth. A complex process of MYC to the uptake of nutrients to make ATP is also essential building blocks that increase cellular growth, activates DNA replication, and causes cell division. This is done through the help of its targets. In the field of translational cancer research shut down checkpoints and let MYC metabolic activities that support cell growth and proliferation loose. Unchecked growth related to dysregulated expression of MYC results in dependence on MYC-dependent metabolic pathways, and this dependence offers new targets for cancer therapy. Activity and expression of MYC are firmly upregulated in normal cells by several phenomena, as well as it depends on the stimulation of growth factor and overfull nutrient status. However, due to the dependence of MYC-driven tumors on already identified metabolic pathways, the synthetic lethal association between overexpression of MYC and certain enzymes gives inhibitors novel therapeutic opportunities. MYC is overexpressed in more than 50% of breast cancer patients, and its expression is connected with a very poor prognosis and a high risk of metastasis. MYC promotes breast cancer development and progression with several mechanisms, as well as the activation of cell proliferation, inhibition of apoptosis, and induction of angiogenesis. MYC also played a deciding role in the resistance to chemotherapy and radiation therapy.

Keywords: Breast cancer, MYC regulation, Breast Cancer Metabolism,

INTRODUCTION

Breast cancer is a common disease worldwide in women, which continues to be a major issue for the health of the public and is a high focus for biomedical research despite significant improvements in the field.[1] Breast cancer is a prevalently diagnosed malignancy in women worldwide and is the reason for many cancer-related fatalities. There are several reasons for the high mortality rate of breast cancer, with metastasis to important organs being the main factor.[2] Research efforts in the past several years have shown that breast cancer demonstrates heterogeneity along with differential metastasis to different organs, starting to cause to differences in potential treatment in responses to therapy of breast cancer patients.[3] The process of development of breast Cancer involves epigenetic and genetic extensive changes that drive the normal cell into tumor one.[4] With a projected 2.3 million novel cases every year, it becomes one of the most common malignancies to be diagnosed and the fifth leading cause of mortality due to cancer worldwide according to the GLOBOCAN data.

The MYC family includes three interconnected human genes: MYC, MYCL, and MYCN.[2] In Breast cancer, c-MYC is frequently expressed. It promotes the simultaneous upregulated expression of various genes, which are involved in cell

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URN:NBN:sciencein.cbl.2025.v12.1266
DOI: 10.62110/*sciencein.cbl.2025.v12.1266*

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proliferation, which leads to the formation of a tumor.[5] Since, 25 years ago introduction of MYC has gone under extensive research, where it seems to be organ-specific, and in cancer, where processes involved contribute to aberrant MYC expression, has been achieved. Many signals and pathways converge on MYC, and MYC then acts via transcriptional and non-transcriptional mechanisms on an ever-increasing number of known targets.[6] The most prevalent type of the three c-Myc proteins, known as MYC," is c-Myc2 which has a mass of about 62 kDa.[7] A review of MYC discussed briefly as a signaling mediator in the mammary gland, which discussed how it functions normally during development and how it is activated and involved in breast cancer regulation.[8] Many signals and pathways connect on MYC, and MYC then acts via transcriptional and non-transcriptional mechanisms on an ever-increasing number of known targets.[7] MYC regulates nutrition uptake to make ATP and important cellular building blocks that increase cell mass, activate DNA replication, and cause cell division through its targets.[9] The source of the life-threatening disease breast cancer can be genetic or sporadic, The majorly reported mutations correlated with hereditary involved cancer to encompass which is going to influence DNA damage repair (DDR) genes, from which mutations in the BRCA1, BRCA2 along with TP53 genes are the most important.[10] PI3K/Akt/mTOR is the main cell signaling that plays a key role in cell `growth, proliferation, metabolism, and immune response regulation.[5] Cell signaling initiated from the tyrosine kinase receptors (RTKs) Her2/Neu and estrogen receptors (ERs), are the two main components of breast cancer progression. Their activation simultaneously increases PI3K/Akt/mTOR and MAPK pathways that promote cell growth, proliferation, survival, and other hallmarks of cancer. Although the study of MYC/PI3K/Akt/mTOR signaling is necessary to explore the different pathways that are connected by different.[11] Two instances are reported: Ras activating PI3K and some mTOR Complex-activated proteins interacting with the MAPK pathway. In addition, GSK-3 has a significant impact on how these pathways are controlled. By inhibiting and activating several molecules connected to the PI3K and MAPK pathways, GSK-3 serves as an illustration of how intricate those relationships are with each other.[12] The PI3K pathway controls glucose uptake and utilization in addition to its well-known function in using mTOR to route available amino acids into protein synthesis.[13] It is well known that MYC activation contributes to the advancement of breast cancer. Because breast cancer is a complex, multifaceted disease, the most significant variables affecting treatment decisions are tumor histology and biochemical investigations.[14] Three primary subtypes of breast cancer are classified as ER, HER2+, and TNBC based on biochemical markers. MYC is elevated in TNBC compared with other cancer subtypes. Aggressive breast cancer cells with a drug-resistant phenotype have increased levels of MYC-driven pathways.[15] Hence, comorbidities and co-mortalities need to be given more attention if we are to successfully combat breast cancer and improve the quality of life for those affected. despite breast cancer being a specific cause of death. Breast cancer patients' exposure to cancer is well known, but research into cause-specific mortality from other causes of death has been less thorough. A significant study may be reported to investigate the therapeutic potential approach of the receptor by targeting the MYC receptor. However, to yet, no clinically meaningful increase in overall survival due to specific suppression of any cancer type has been documented.

Warburg Effect and Breast Cancer

Cancer cells have strangely different metabolic priorities as compared to normal cells so this strategy provides a novel idea regarding the therapeutic approach. Reprogramming of metabolic pathways in cancer cells helps in growth and maintenance. Through scientist Otto Warburg, a Large amount of lactate production was seen in tumors even when sufficient oxygen was present and this process is known as this phenomenon is called the Warburg effect or aerobic glycolysis.[16] Increased hormone exposure, with early maturity, late menopause, high alcohol consumption, prolonged lactation, and obesity are linked with a high risk.[17] One of the globally known attributes of the tumor metabolic process is glycolysis especially in aerobic conditions (The Warburg effect) as mentioned in figure 1. A typical metabolic adaptation of aerobic glycolysis relies more and more on increased glucose absorption, glycolytic metabolism, and lactate generation even in aerobic settings condition.[18] This biological process provides information about several anabolic intermediates that generate energy and act as anabolic precursors to support the accelerated growth of tumor cells, particularly during hypoxic circumstances.[19] MYC plays a crucial part in the control of aerobic glycolysis. By binding to the traditional E-box region, MYC triggers the transcription of practically all glycolysis-related genes. One of the glucose transporters GLUT1 (Glucose Transporter-1) is reported as the target of MYC, this transporter is upregulated through MYC to increase the intake of glucose for further glycolysis.[20] An assay of Chromatin immunoprecipitation stipulates that hexokinase II (HK2), enolase 1 (ENO1), and lactate dehydrogenase A (LDHA) which is associated with MYC on the E-box spanning different species.[21] MYC also helps in the export of lactate with the help of monocarboxylate transporters, MCT1 and MCT2, to enhance levels of lactate inside the tumor cells.[2223] In gene expression, in addition, MYC affects the genes glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and triose phosphate isomerase (TPI), regardless of the absence of classical E-boxes around their promoters. This suggests that MYC indirectly controls these genes.[24] MYC has been shown to activate glycolytic genes by alternative splicing in addition to transcription. In contrast to PKM1, which appears to promote oxidative phosphorylation, pyruvate kinase type M2 (PKM2) helps in the final stage of aerobic glycolysis.[25] Mitochondria are the most important organelles not only because their primary work like oxidative phosphorylation produces ATP and respiration but also due to they provide a huge center for different types of pathways (biosynthetic), like a synthesis of nucleotide, fatty acid, cholesterol, amino acid, and of heme.[26] The transferrin receptor, or TFRC, is a crucial MYC-responsive gene that imports the iron needed for mitochondrial activity, which is necessary for cell

proliferation.[27] In a cell most preferably, mitochondria directly affect the overall rate of transcription.[25] Whenever a cell division helps in cell growth then an increment in the number of mitochondria is also found. The process through which mitochondrial biogenesis occurs in response to cell growth is not as well understood as the factors that control it for homeostasis. simultaneously increases the glycolysis in terms of lactate production with the help of MYC has only recently been proposed. It was observed that MYC promotes transcription of splicing factors to raise the level of the expression of (pyruvate kinase M2) PKM2 over (pyruvate kinase M1) PKM1, hence to promote glycolysis.[25] An important chunk of data gives information about the Inhibition of PKM2 might enhance the drug tolerance of cancer cells. Contact of PKM2 which restricts PKM2 activity by augmenting its phosphorylation at threonine 105, with substantial ROS production, and boosting cisplatin sensitivity in cancer cells. Moreover, the elimination of CD44 leads to a switching of aerobic glycolysis into the TCA cycle and an increase in ROS generation, which improves cancer cells' sensitivity to cisplatin.[28] The crucial transcription factor hypoxia-inducible factor (HIF)-1, in addition to MYC, is in charge of promoting glycolysis in tumor cells in hypoxia conditions. Both MYC and MYCN interact with HIF-1 to promote the expression of essential glycolytic genes with concern to hypoxia, including HK2 and pyruvate dehydrogenase kinase 1 (PDK1) in MYC-driven Burkitt's lymphoma cells and LDHA in MYCN-amplified tissue of neuroblastoma. This shows the binding of MYC oncoproteins and HIF-1 is crucial for the upregulation of glucose metabolism in malignancies.[29]

MYC in Fatty Acid Synthesis and Amino Acid Synthesis

Lipids constitute vital components of cell membranes, signaling molecules, and energy stores. Cancer cells, particularly those with MYC overexpression, have increased de novo fatty acid synthesis in order to encourage rapid expansion. MYC regulates key enzymes that contribute to fatty acid and cholesterol synthesis, ensuring a consistent supply of lipids for tumor growth. One of the most important MYC-regulated enzymes is ATP-citrate lyase (ACLY), which turns citrate into acetyl-CoA, a precursor for fatty acid and cholesterol production. MYC also increases the expression of acetyl-CoA carboxylase (ACC), the enzyme that converted acetyl-CoA into malonyl-CoA, which is the first committed step in fatty acid synthesis.[30] Additionally, MYC upregulates **fatty acid synthase (FASN)**, which catalyzes the formation of long-chain fatty acids required for membrane synthesis and oncogenic signalling. Stearoyl-CoA desaturase (SCD), a vital component MYC target in lipid metabolism, converts saturated fatty acids to monounsaturated fatty acids. These monounsaturated fatty acids are required for membrane fluidity and function, allowing cancer cells for efficient propagation. Furthermore, MYC-driven lipid production is associated with resistance to lipid peroxidation, which protects cancer cells against oxidative damage[31] and ferroptosis, a type of programmed cell death.[32]

Many cancer cells require metabolic reprogramming to proliferate over an extended period. While glycolysis and glucose transport are widely accepted, MYC's involvement in amino acid metabolism is equally critical. MYC, a master transcription factor, stimulates key amino acid transporters including SLC1A5 (ASCT2), which aids in the absorption of glutamine and other nutrients. In cells, glutamine is transformed to glutamate and α-ketoglutarate, which fuel the tricarboxylic acid cycle and act as building blocks for macromolecule synthesis.[33] MYC regulates enzymes that produce non-essential amino acids like serine and glycine, which aid in nucleotide production, protein synthesis, and redox balance. Furthermore, feedback linkages with enzymes such as glutaminase strengthen these metabolic changes, increasing tumor growth. Addressing glutamine uptake and metabolism may disturb the metabolic flexibility of MYC-driven malignancies, making MYC an important target for anticancer treatments. Overall, these findings add to our understanding of cancer metabolism

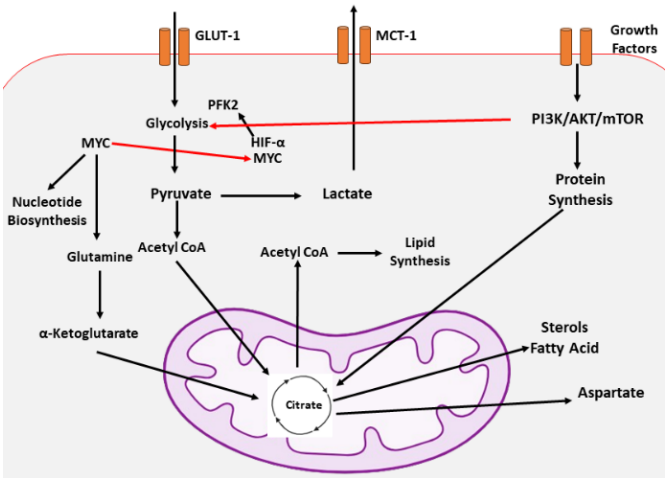

Figure 1: Mechanism-based control of metabolic changes. The metabolic changes associated with breast cancer are attributed to the metabolism of glucose, lipids, and proteins.

STRUCTURAL INFORMATION OF MYC

MYCs have been reported as critical regulators of cell proliferation, differentiation, apoptosis, and metabolism. MYC deregulation is the main factor that contributes to the development of breast cancer progression and it is connected to very low outcomes. MYC was initially found as they have cellular homology of the retroviral v-MYC which is also reported as an oncogene.[9,34] Several procedures are taking part where deregulation of MYC in breast cancer, along with mRNA, protein stabilization, amplification of the gene, and also the regulation of the transcription process, which eventually leads to loss of tumor suppression and promotes oncogenic pathways.[35] Similar to its relatives N-MYC and L-MYC, c-MYC (which is why they are abbreviated as "MYC") is a transcription factor that dimerizes working together with MAX to establish a bond with DNA to regulate the expression of genes.[36] To establish a significant target for the cancer therapy the c-MYC was considered because its role was reported as a major transcription factor along with the ultimate promoter of cell growth and proliferation. it has been given thought as an important target for the treatment of cancer. This basic helix−loop−helix Zip protein makes a heterodimer with its companion MAX, this complex binds to a basic region of

DNA. Impressive exploration endeavors are centered around focusing on the interface heterodimerization and the association of this structure with DNA. The basic crystal structure of the c-MYC: MAX complex has been bound to DNA artificially and connected by a disulfide linker bond. The intrinsically disordered transcription factors c-MYC correspond to the basic helix-loop-helix zipper (bHLHZip) family. The N-terminal transactivation domain (NTD), the C-terminal domain (CTD), and the middle region are made up of 439 amino acids (aa). The main basic input needed for the survival and proliferation of normal cells integrated by the c-MYC pleiotropic transcription modulator.[4,37] c-MYC facilitates the expression of an immense, diversified arrangement of genes in a way context-dependent manner and it also acts as both transcriptional activator and repressor.[11,23] These regulate extracellular processes that coordinate cell proliferation with its surrounding somatic microenvironments, such as angiogenesis, invasion, stromal remodeling, and inflammation, as well as intracellular processes that control cell growth, cell cycle progression, biosynthetic metabolism, and apoptosis.[38] Structural information helps to predict the related information of particular protein to develop therapeutic approach.

Structure analysis of MYC along with FASTA Sequence (PDB ID: 6G6K)

C-MYC, N-MYC, and L-MYC are three closely related nuclear phosphoproteins that belong to the MYC family of cellular proto-oncogenes. Related genes of these three are located on chromosome 8, chromosome 2, and chromosome 1. The structural analysis of MYC reported there is no protein encoded by the first exon present while analysis third exon that found to encode a protein. The MYC gene comes under the oncogene family that encodes a nuclear protein associated with a nuclear DNA binding protein that participates in the regulation of the cell cycle. Enhancing operations like the proliferation of cell dedifferentiation, and transformation along immortalization is mostly carried out by a family of MYC genes and related products The main crucial reason to classify p62c-myc (phosphorylated), as a nuclear protein is that it is a co-product of the C-MYC and having region of non-specific DNA binding, a target sequence, a basic helix-loop-helix (HLH) along with a leucine zipper region, among known transcription factors.[39] This is the unique feature of this protein that the presence of these two regions in MYC protein facilitates the binding with Max. The alkaline nature of MYC and helix-loop-helix gives contribution towards binding with DNA.[40,41] A study reported in prokaryote special phenomena involved in the formation of helix from a basic structure to binds with the specific region of DNA.[42] The native protein C-MYC is a known transcription factor characterized as bHLHLZ (basic region/helix-loop-helix/leucine zipper) which links to a particular kind of electronic box to create a long sequence that is 5'-CACGTG-3'. These are detailed structural information about MYC genes.

Regulation of MYC Signaling in Breast Cancer

Severe molecular mechanisms are involved in the dysregulation of MYC like an amplification of gene and mRNA and protein stabilization, and loss of tumor suppression by the activating oncogenic pathways MYC participates in the development of breast cancer as mentioned in the figure 2.[43] Overexpression of MYC in the subtype of basal-like may act as a target for this highly active subtype of breast cancer.[19,44] One of the main mechanisms through which MYC promotes the development and progression of breast cancer through its effect on cell signaling pathways. MYC helps to promote several signaling pathways, like the PI3K/Akt, MAPK/ERK, and Wnt/β-catenin pathways, and all are involved in cell proliferation, survival, and differentiation of the cell. MYC also interacts with other signaling molecules, such as the tumor suppressor p53, to promote tumor growth and survival and it is a key regulator of cell growth, and proliferation.[45,46] Several studies have been performed to know the role of MYC in breast cancer cell signaling, and several potential therapeutic targets have been identified. For instance, inhibition of the PI3K/Akt signaling was explored to sensitize breast cancer cells to chemotherapy and radiation. Similarly, targeting the MAPK/ERK pathway by cell cycle arrest and apoptosis in breast cancer cells. Moreover, targeting MYC itself using small-molecule inhibitors or RNA interference has shown promising results in preclinical studies.[47] Growth factors can cause tremendous enhancement to become activators of enhancers in noncancerous cells. Activation of mTOR highly influenced the translational pattern of MYC which eventually dimerizes with the structure of MAX to form a heterodimer which leads to an increase in transcription of gene present in high-affinity E-boxes.[19,48] There are so many reasons to prevent the dimerization of MYC/MAX for example lack of nutrition and hypoxia is also responsible for this. P53 and ARF checkpoints are also activated due to hyperactivation of MYC which eventually leads to cell death or arrest but apart from that ARF can inhibit the function of MYC. Downstream of AKT, FOXO3A proteins counteract MYC activation.[49,50] The simultaneous activation of different types of growth factors along

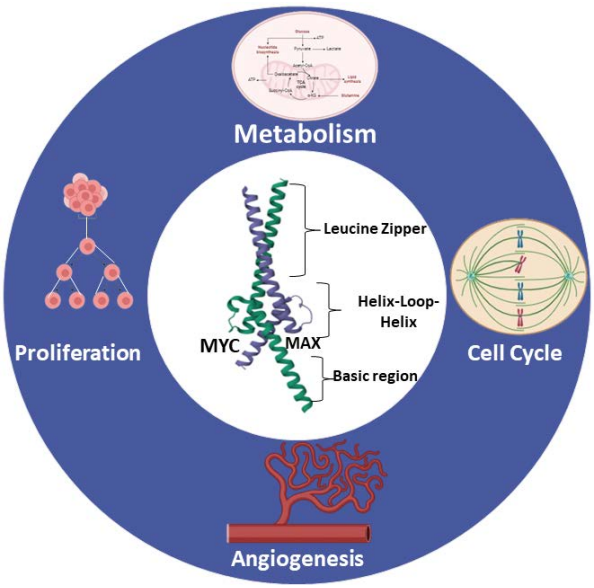

Figure 2: Structural representation of MYC which heterodimerized with partner MAX which helps to regulate cell proliferation, cell cycle, metabolism and angiogenesis.

with mTOR signaling, involvement of typical enhancers or amplification, loss of checkpoints, and loss of ARF or p53 activity can increase the amount of MYC in cancer cells allowing uncontrolled cell growth.[51,52] Overexpression of MYC and eIF4E increases the cap-dependent translation and a study reported analysis through PCR compared eIF4E and eIF2A MYC expression levels in cells.[4,53] ATF6, IRE1, and PERK represent the three main transducers of unfolded protein responses (UPR), which emerge in response to multiple intracellular and outside forces that disrupt protein folding in the endoplasmic reticulum (ER). Human diseases such as cancer and different metabolic syndromes have been shown to be influenced by endogenous stress.[7,54] Pro-apoptotic and pro-survival characteristics are shared by PERK, a type I protein kinase located in the endoplasmic reticulum (ER). By modulating cancer gene expression through its downstream substrates, it functions as a coordinator to enhance survival in the face of oncogenes and microenvironmental obstacles like as metastasis, hypoxia, and angiogenesis. Enzyme kinase R-like the endoplasmic reticulum kinase (PERK), inositol requiring enzyme 1 alpha (IRE1α, ubiquitous), inositol that demands enzyme 1 beta (IRE1β, tissue-specific), and triggering transcription factor 6 (ATF6) are a number of transmembrane signal transducers in the ER membrane that the initiate the unfolded protein response (UPR), a coordinated signaling pathway.

These major sensors are normally bound and kept inactive by the molecular chaperone BiP/GRP78 in the ER membrane. However, ER stress triggers the dissociation of these sensors from BiP, leading to their conformational change and activation for

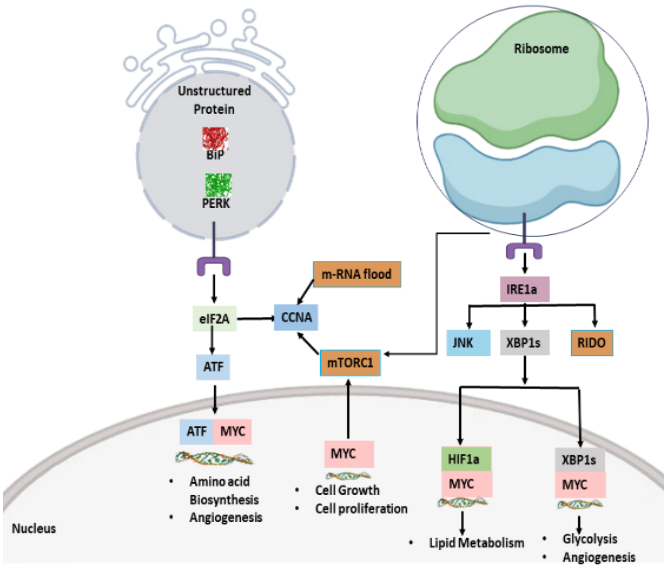

Figure 3: MYC and downstream signaling pathways activated through interaction with other genes. I n endoplasmic reticulum pathways activated through MYC interaction with ATF which finally helps in the synthesis of Amino acid along with angiogenesis. In Ribosomes there are different types of pathways are involved for example IRE1a interacts with HIF through the mediator gene XBP1s which helps in the enhancement of Glycolysis and angiogenesis. With the help of mTOR pathway MYC helps in increasing cell growth and proliferation.

downstream signaling.[55] The association of MYC with ATF promotes amino acid biosynthesis and enhances angiogenesis. The MYC promoter have different binding sites for various transcription factors, including MYC, Notch/C promoter-binding factor 1 (Cbf1), E2F, Fos/Jun, signal transducer which helps to promote transcription of (STAT3), NF-κB, Smads, and others. Some transcription factors, such as p53, CCAAT/enhancer binding protein beta, and also Stat5, can also regulate the MYC promoter without specific binding sites.[11] Additionally, several signaling pathways frequently deregulated in human cancer, such as Ras/extracellular signal-related kinase (Erk) and phosphoinositide 3-kinase (PI3K)/serine/threonine kinase Akt (Akt), can influence MYC expression.[56] Research using pharmacological inhibitors and maintaining both dominant-inhibitory and wild-type versions of Akt revealed the function of PI3K in polypeptide growth factor receptor-mediated apoptosis suppression, suggesting that Akt mediates PI3K-dependent survival.[57] In response to ER stress, the type I single-pass transmembrane protein IRE1 oligomerizes and trans-autophosphorylates. IRE1 contains an RNase domain that selectively degrades mRNA, microRNA, and ribosomal RNA in an IRE1-dependent decay (RIDD) pathway. Xbp1 mRNA, a transcriptional regulator, is the major substrate of IRE1. Gene expression connected with folding of proteins, secretion, and endoplasmic reticulum-associated degradation (ERAD) can be influenced by spliced Xbp1.[58] A study revealed that MYC typically controls the transcription of IRE1 by binding to its enhancer and promoter. Moreover, MYC stimulates the transcriptional function of IRE1's target, XBP1, by forming a complex with it. Importantly, because silencing XBP1 inhibited MYC-hyperactivated cell types from expanding, researchers speculated that XBP1 is a deadly synthetic partner of MYC.[26] The PI3K/Akt and JNK signaling pathways play critical roles in regulating various cellular processes such as cell growth, invasion, and apoptosis, and are involved in tumor development and progression.[10] The interplay between these pathways is complex, with the dual functions of JNK signaling in apoptosis and tumorigenesis influencing their interactions. Activation of PI3K/Akt signaling can inhibit the activation of JNK induced by stress and cytokines, due to the antagonistic relationship between Akt and PI3K/Akt signaling and the formation of the JIP1-JNK module.[59] Regulation of signaling by targeting MYC has a great potential for drug discovery.

PHYTOCHEMICAL ENHANCES THERAPEUTIC IMPORTANCE THROUGH TARGET

Breast cancer [BC] is a disease that affects women worldwide and is a significant contributor to healthcare costs in both developed and developing countries. BC has repeatedly demonstrated resistance to chemotherapy, radiation therapy, and hormone treatment. It is critically necessary to develop new, affordable, and widely available therapeutic approaches. Since plant-derived molecules are often physiologically active, there is a growing interest in these compounds within science. Several in vivo and in vitro studies have suggested a potential role in reducing the incidence of cancer metastasis. Many metabolic and

molecular processes, such as the regulation of the cell cycle, the induction of apoptosis, angiogenesis, and the prevention of cancer metastases, are believed to be regulated by a multitude of phytochemicals. Phytochemicals exhibit an extensive range of preventive or disease-preventing properties. Since ancient times, they have been used to treat various diseases, such as diabetes, cancer, heart disease, inflammatory processes, neurological conditions, and skin conditions.[60] According to several epidemiological studies, utilizing phytochemicals may lower the risk of cancer.[34] The alkaloid, known as bis-benzylisoquinoline, is found in the Chinese herb Berberis amurensis. High anticancer applications and other beneficial properties have been linked with berbamine and its analogs. Triple-negative breast cancer is an aggressive form of the disease, and berberine has been shown to have anticancer properties against it. Berbamine was added to MDA-MB and MCF-7 cell lines at varying doses.[61] Terpenoids made an important advancement in the field of cancer treatment with the 1993 approval of Taxol®, an agent that is still vital for treating ovarian, breast, and other resistant malignancies. Other well-known natural terpenoids have grown to be essential throughout the years to the contemporary pharmacotherapy of breast cancer. Effective therapies for advanced breast tumors needing cytotoxic chemotherapy, however, constitute an important unmet clinical need given the rapid development of drug resistance.[62] Fruits, vegetables, tea, essential oils, and cereals have plenty of sources of polyphenols because they contain one or more phenolic rings that have been replaced with at least one hydroxyl group. The primary structural variability among the numerous classes and subclasses of polyphenols is provided by the number of phenolic rings and the moieties that substitute their aromatic rings. Breast cancer cells exhibit decreased proliferation and an increase in apoptosis as a result of tea polyphenols, such as epigallocatechin gallate (EGCG), downregulating telomerase activity in these cells. They can also impede cell development and initiate apoptosis by downregulating the expression of survivin, a protein belonging to the inhibitor apoptosis protein family (IAP) that inhibits caspases and slows down cell death.[63] Research from both epidemiological and lab settings has suggested that consuming certain organosulfides may help avoid cancer. Such compounds are found in nature, especially in a lot of plant-based diets. Several organosulfides have also been acknowledged as safe food additives by the general public.[64] Cancer cells are characterized by the aberrant activation or suppression of proto-oncogene and tumor suppressor genes, respectively. Tumor cells have evolved through a variety of processes, such as immortalization, enhanced angiogenesis, prolonged proliferation, growth suppressor inactivation, metastasis, and resistance to programmed cell death.[65] In healthy tissues, growth-promoting signals are tightly controlled to maintain cellular homeostasis; in cancer cells, on the other hand, these biological signals are dysregulated. The very simplified pathways show important steps that occur both upstream and downstream of the MYC oncoprotein. Through guanine nucleotide exchange factors, activated tyrosine kinase receptors (RTK) transfer signals onto the G protein RAS to start the mitogenic signal transduction process. The serine/threonine protein kinase RAF is bound and activated by RAS, which controls the expression of several target genes.[66] Subsequently, this process involves the successive phosphorylation of factor complexes such as MYC/MAX or JUN/FOS (AP-1), mitogen-activated protein kinase (MAPKK) MEK, and MAP kinase. The synergy between MYC and RAF(Mil) suggests that a positive feedback loop may be responsible for the increase of RAS/RAF-induced cell transformation by specific MYC targets.[67] However, MYC might be able to directly activate AP-1 by stimulating the transcription of FOS or JUN-encoding genes. The c-MYC gene experiences transcriptional activation.[68] The control of the cell's life cycle and the promotion of fast cell proliferation are two functions of several transforming MYC targets, which encode transcription factors such as E2F and cyclins (CCN) and cyclin-

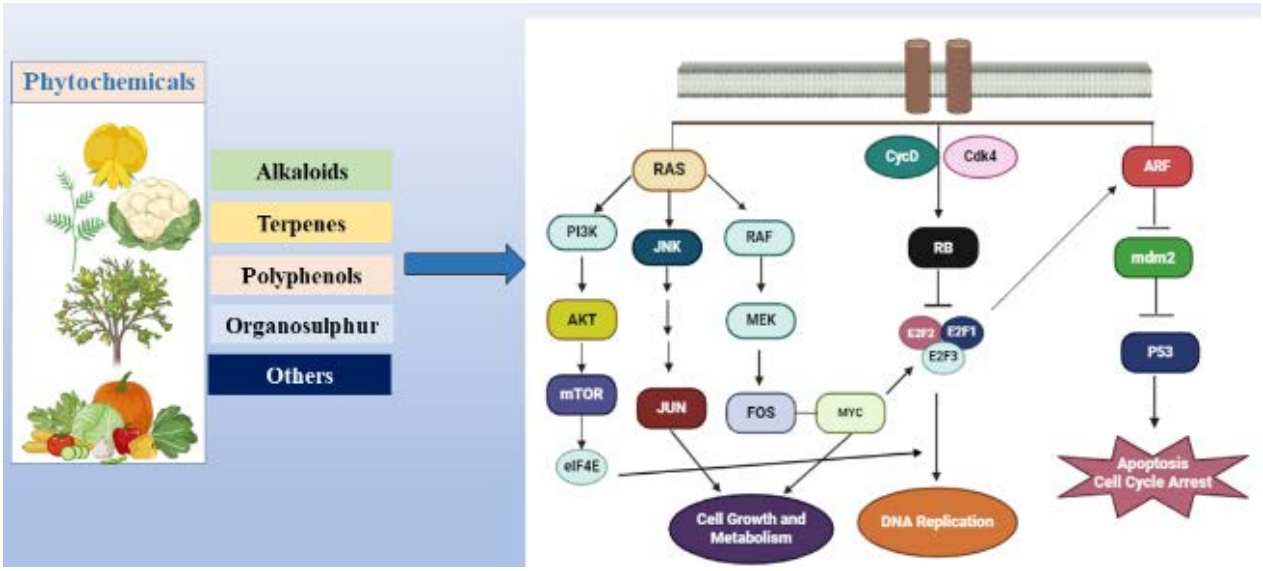

Figure 4: Schematic representation of signaling pathways/ factors possibly regulating 1q candidate gene expression in breast cancer. EGFR, RAS, PI3K / AKT, MYC, and E2F were identified as the upstream regulators of these genes

dependent kinases (CDK).[69] A major mechanism controlling cell growth, proliferation, and survival in response to external stimuli is phosphatidylinositol 3-kinase (PI3K)–mammalian target of rapamycin (mTOR) signaling, in addition to the extracellular signal-regulated kinase (RAS–ERK) pathway. Protein kinase AKT phosphorylates various survival factors, and mTOR-mediated signaling controls the translation of proteins that support cell growth and proliferation, like cyclin D and c-MYC, and ribosome biogenesis.[70]

MYC-targeting medications have emerged as an achievable option for cancer treatment, nonetheless clinical translation is difficult due to MYC's exacerbated biochemistry. Direct suppression of MYC is notoriously difficult due to its gradually disordered structure and lack of a catalytic domain, which prohibit average small molecule binding. As a result, being here tactics rely primarily on indirect approaches. One such strategy involves inhibiting bromodomain and extraterminal domain (BET) proteins, which are crucial for MYC transcription.[71] Compounds like JQ1 and OTX015 have demonstrated the ability to reduce MYC expression by disrupting the binding of BET proteins to acetylated histones. Another approach targets the MYC–MAX interaction, essential for MYC's transcriptional activity. Small molecules such as 10058-F4 have been developed to disrupt this interaction, although issues with pharmacokinetics and bioavailability have limited their clinical progression. Emerging approaches also include influencing upstream regulators that impact MYC stability. To boost MYC breakdown, proteolysis-targeting chimeras (PROTACs) and inhibitors of kinases involved in MYC phosphorylation are being investigated.[72] Despite these advancements, difficulties exist. The ubiquitous function of MYC in ordinary cellular proliferation raises considerable concerns regarding on-target toxicity and a limited treatment window. Furthermore, tumor heterogeneity and compensatory signaling pathways may help to establish resistance. To deal with these issues, combination medicines are being developed. Combining MYC-targeting medicines with metabolic inhibitors or other anticancer treatments may increase efficacy while avoiding resistance. Identifying predictive biomarkers is also vital to patient classification and treatment regimen optimization. Further study into MYC biology and new drug delivery systems will be critical to turning these medicines into effective clinical treatment. MYC not only promotes cellular proliferation and metabolism, but it also controls metastasis and the tumor microenvironment (TME). MYC has been found in the setting of metastasis to modulate the expression of genes involved in epithelial-to-mesenchymal transition (EMT), a critical mechanism that increases cancer cells' migratory and invasive capacity.[19] MYC promotes tumor cell proliferation by upregulating EMT markers such as N-cadherin and vimentin while downregulating epithelial markers such as E-cadherin. MYC also impacts the TME by regulating a network of signaling compounds, cytokines, and growth factors that change the surrounding stroma. For example, MYC-driven tumors regularly secrete more pro-inflammatory cytokines and chemokines, which attract immunosuppressive cells such tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs). This recruiting not only aids in immune evasion but also stimulates angiogenesis through molecules such as vascular endothelial growth factor (VEGF), resulting in an environment favourable to tumor development and spread. Additionally, MYC impacts the extracellular matrix (ECM) by upregulating matrix metalloproteinases (MMPs), which degrade ECM components, facilitating tumor cell invasion and metastasis. MYC's modulation of stromal cell behavior, including that of cancer-associated fibroblasts (CAFs), further contributes to the dynamic crosstalk within the TME, enhancing structural changes that favor tumor spread.[73]

In a nutshell MYC's influence extends far beyond metabolic reprogramming, regulating both cancer cells' intrinsic features and their interactions with the microenvironment. This diverse role emphasizes the significance of considering into account MYC's direct and indirect actions when developing therapeutic strategies to limit metastasis and modify the tumor microenvironment. In breast cancer, MYC overexpression is caused by a complex combination of transcriptional and post-transcriptional mechanisms that are frequently regulated by important signaling pathways. At the transcriptional level, oncogenic signaling via PI3K/AKT and MAPK/ERK is valuable. For example, in HER2-positive and luminal subtypes, receptor tyrosine kinase activation activates these pathways, resulting in the activation of transcription factors.[74] These components interact to the MYC promoter region, stimulating its transcription. The Wnt/β-catenin pathway, which is typically active in basal-like and triple-negative breast carcinomas, stabilizes and relocates β-catenin, which binds to regulatory areas of the MYC gene, increasing its expression. RNA-binding proteins and microRNAs closely regulate MYC mRNA stability and interpretation after transcription. In breast cancer, deregulation of microRNAs such as the let-7 family, which typically inhibit MYC translation, can result in elevated MYC protein levels. Furthermore, increased mTOR signaling downstream of PI3K/AKT can facilitate MYC mRNA translation.

Additional cellular processes include MYC gene amplification, which is very prevalent in triple-negative carcinomas of the breast and directly raises MYC dose. Mutations or deletion of the E3 ubiquitin ligase FBW7 contribute to MYC protein buildup by slowing proteasomal breakdown. These transcriptional activations and post-transcriptional modifications work together to drive MYC overexpression, emphasizing MYC's complex regulation specifically breast cancer subtypes and suggesting new therapeutic treatments.

Preclinical studies have provided promising evidence that targeting MYC or its associated pathways can inhibit tumor growth in breast cancer models. For example, small molecules designed to disrupt the MYC–MAX interaction, such as 10058-F4, have shown efficacy in reducing proliferation and inducing apoptosis in MYC-driven breast cancer cell lines. However, these direct inhibitors often suffer from poor pharmacokinetic properties, limiting their clinical translation.[75] Indirect approaches, notably BET inhibitors like JQ1 and OTX015, have garnered considerable attention. BET inhibitors work by

impairing bromodomain protein function, thereby downregulating MYC transcription. Preclinical models, particularly in triple-negative and HER2-positive breast cancers, have demonstrated that BET inhibition can suppress MYC expression, reduce tumor growth, and sensitize cancer cells to chemotherapy. Early-phase clinical trials of BET inhibitors have been initiated, though patient selection and resistance remain areas of active investigation.[76] Targeting MYC-driven metabolic pathways is another attractive approach. MYC overexpression in breast cancer alters metabolism, specifically via increasing glutaminolysis and changing nucleotide biosynthesis. Glutaminase inhibitors, such as CB-839 (Telaglenastat), have demonstrated preclinical efficacy by deprived MYC-driven cancers of glutamine, resulting in reduced proliferation and enhanced apoptosis. Additionally, treatments aimed at altering serine and glycine production pathways are being looked into, counting on MYC's roles in metabolic reprogramming. Some of these metabolic inhibitors are now being tested in clinical trials as monotherapies or in combination with other targeted medication, with the aim of exposing the metabolic vulnerabilities found exclusively in MYC-driven malignancies.[77] Despite these advancements, direct targeting of MYC remains difficult due to its "undruggable" structure, potential harmful effects in normal tissues, and compensatory signaling pathways that could promote resistance. These constraints highlight the requirement for combination tactics and strong biomarker research to optimize patient selection and improve therapy results in breast cancer.

TARGETING BREAST CANCER: MANAGEMENT AND TREATMENT

The current treatments for Breast cancer, which include whole-breast therapy, chemotherapy, stereotactic radiosurgery, and surgical resection, have poor success rates. Many breast-related factors, including multiple metastatic lesions, are detrimental to the investigation of highly tumor-specific therapeutics that can address current issues by reducing the likelihood of breast tissue damage and enhancing patient clinical services.[78] Many breast-related factors, including multiple metastatic lesions, are detrimental to the investigation of highly tumor-specific therapeutics that can address current issues by reducing the likelihood of breast tissue damage and enhancing patient clinical services. Therapeutic implication through targeting MYC is the best way to provide health care in the field of medical science. These are some drugs having antitumor activity by targeting MYC and acting as an inhibitor.[79,80] Therefore, this has dwelled the prospects to examine the rate-limiting stages as they could perhaps hypothesize about different targets associated with cancer cell dormancy, survival, proliferation, and recurrence inside the cell.

NCT No.	Status	Condition	Intervention	Study (Phase2)
NCT06185205	Recruiting	Breast Cancer	Procedure: Accelerated partial breast irradiation	2-12-2023 (Phase 2)
NCT06429761	Not Recruiting	Breast Cancer	Drug:	30-9-2024 (Phase 4)
NCT02462200	Terminated	Breast Cancer	Trastuzumab deruxtecan Procedure: Breast-conserving surgery (BCS) + Cavity shave margins (CSM)	13-6-2016 (Phase 2)
NCT01591746	Completed	Neoplasm Breast Cancer	Drug: Botulinum Toxin TypeA Placebo	8-2012 (Phase-3)
NCT03346161	Completed	Breast Cancer	Procedure: Plastic Surgery	09-1-2018 (Phase-1)
NCT01556243	Completed	Breast Cancer	Procedure: Conventional surgery	07-2012 (Phase-1)
NCT01522300	Terminated	Mammary Tumor	Procedure: Tomosynthesis	01-2012 (Phase-2)
NCT04532177	Active, Not Recruiting	Breast Cancer	Procedure: Stereotactic Boc Radiation Therapy	19-8-2020 (Phase-1)
NCT04067726	Recruiting	Dense Breast	Denosumab + Placebo + Calcium	27-8-2019 (Phase-2)
NCT01110954	Terminated	Breast Tumor	PD L 506	31-5-2010 (Phase-2)
NCT04852419	Completed	Breast Neoplasm	ZN-c5	31-5-2021 (Phase-2)
NCT02642094	Terminated	Breast Cancer	Rapamycin	07-2016 (Phase-2)
NCT04193722	Completed	Breast Canc Radiation Toxicity	Hyperbaric oxygen therapy	28-8-2019 (Phase-3)
NCT00206414	Terminated	Breast Cancer	Drug: Arimidex + Faslodex	1-2003 (Phase-2)
NCT03712956	Active Not Recruiting	Breast Cancer	Drug: **Caelyx®**	25-3-2016 (Phase-2)
NCT00558545	Terminated	Mammary Carcinoma	Drug: AEG35156	11-2007 (Phase-2)
NCT05498311	Recruiting	Intraoperati Breast Cancer	Procedure: Radiotherapy, surgery	10--2016 (Phase-2)
NCT00133796	Terminated	Breast Cancer	Procedure: Herceptin	10-2001 (Phase-2)
NCT03844685	Completed	Breast Cancer	Drug: Promensil Placebo Oral Tablet	5-7-2012 (Phase-2)
NCT00002582	Completed	Breast Cancer	Drug: Cyclophosphamide + doxorubicin hydrochloride	6-1993 (Phase-3)
NCT00002585	Completed	Breast Cancer	Drug: pyrazoloacridine	2-1994 (Phase-2)

NCT03863457	Recruiting	Breast Cancer	Drug: Fluoroglutamine [18F]F-GLN	4-5-2019 (Phase-1)
NCT00558545	Terminated	Mammary Carcinoma	Drug: AEG35156	11-2007 (Phase-2)
NCT05498311	Recruiting	Intraoperati Breast Cancer	Procedure: Radiotherapy, surgery	10--2016 (Phase-2)
NCT00133796	Terminated	Breast Cancer	Procedure: Herceptin	10-2001 (Phase-2)
NCT03844685	Completed	Breast Cancer	Drug: Promensil Placebo Oral Tablet	5-7-2012 (Phase-2)
NCT00002582	Completed	Breast Cancer	Drug: Cyclophosphamide + doxorubicin hydrochloride	6-1993 (Phase-3)
NCT00002585	Completed	Breast Cancer	Drug: pyrazoloacridine	2-1994 (Phase-2)
NCT03863457	Recruiting	Breast Cancer	Drug: Fluoroglutamine [18F]F-GLN	4-5-2019 (Phase-1)
NCT05856773	Recruiting	Breast Cancer	Proton Therapy	2- 2024 (Phase-3)
NCT05498311	Recruiting	Intraoperati Breast Cancer	Procedure: Radiotherapy, surgery	10--2016 (Phase-2)
NCT00133796	Terminated	Breast Cancer	Procedure: Herceptin	10-2001 (Phase-2)
NCT03844685	Completed	Breast Cancer	Drug: Promensil Placebo Oral Tablet	5-7-2012 (Phase-2)
NCT00002582	Completed	Breast Cancer	Drug: Cyclophosphamide + doxorubicin hydrochloride	6-1993 (Phase-3)
NCT00002585	Completed	Breast Cancer	Drug: pyrazoloacridine	2-1994 (Phase-2)
NCT03863457	Recruiting	Breast Cancer	Drug: Fluoroglutamine [18F]F-GLN	4-5-2019 (Phase-1)
NCT05856773	Recruiting	Breast Cancer	Proton Therapy	2- 2024 (Phase-3)
NCT02679040	Active Not Recruiting	Breast Cancer	Procedure: Chemotherapy	27-1-2016 (Phase-2)
NCT00133796	Terminated	Breast Cancer	Procedure: Herceptin	10-2001(Phase-2)

DISCUSSION AND FUTURE PERSPECTIVE

MYC is reported as a confounding oncogene for the reason it appears to have an impact on cellular function including cell signaling and cellular metabolism. This enigma could be solved at the molecular level by indicating events that suggest MYC is a general enhancer of gene expression. with its targets determined by the affinity of binding site sequence and chromatin accessibility and its symmetry and impact determined by the transcriptional capability of gene loci that are co-regulated by different transcription factors.[81,82] The current treatments for Breast cancer, which include whole-breast therapy, chemotherapy, stereotactic radiosurgery, and surgical resection, have poor success rates. Many breast-related factors, including multiple metastatic lesions, are detrimental to the investigation of highly tumor-specific therapeutics that can address current issues by reducing the likelihood of breast tissue damage and enhancing patient clinical services.[82,83] Many breast-related factors, including multiple metastatic lesions, are detrimental to the investigation of highly tumor-specific therapeutics that can address current issues by reducing the likelihood of breast tissue damage and enhancing patient clinical services. Therapeutic implication through targeting MYC is the best way to provide health care in the field of medical science. These are some drugs having antitumor activity by targeting MYC and acting as an inhibitor.[84] Therefore, this has dwelled the prospects to examine the rate-limiting stages as they could perhaps hypothesize about different targets associated with cancer cell dormancy, survival, proliferation, and recurrence inside the. Every cell, along with stem cells has metabolic activity and basally expresses metabolic genes with open chromatin in the system. Thus, quiescent stem cells in the proliferative system of tissues are self-assessed to proliferate upon stimulation by growth factors that trigger MYC expression.[10] In this activation of MYC, genes, that are already functional are amplified to meet the growing cell bioenergetic demands when they depart from the pool of stell cells and differentiate with cell lineage.[85] MYC is restrained in this kind of function not only by the presence of growth factor but also by the availability of nutrients. However, appears that its aberrant metabolic genes are already under the control of endogenous MYC but also seem to invade sequences of enhancers that additionally increase gene expression in a nonlinear manner.[86] Because of the skewed gene-expression amplification, non-stoichiometric expression, the unfolded protein response (UPR) pathway initiation, and dependence on, MYC overexpressing cells are vulnerable to lethality (synthetic) when specific metabolic pathways are inhibited.[87,88] Here, basic scientific investigation into cancer metabolism has resulted in several novel discoveries of therapeutic potential that may progress cancer treatment. The field is now looking to the future for new medication and treatment methods that can have a positive clinical impact. In conclusion, MYC's impact on cell signaling pathways eventually contributes to the rapid enhancement and spread of Breast cancer.[85] The identification of MYC as a critical driver of breast cancer has led to the development of several therapies that promise to improve breast cancer outcomes. However, further research is needed to fully understand the complex interplay between MYC and other signaling molecules and to develop effective and safe targeted therapies for breast cancer patients. The role of MYC has been identified as a key enhancer of cell signalling which eventually helps in cell growth. E-box is considered a regulatory element of genes and is found in the genome with around 1000 nucleotide high frequency.[89] MYC gene amplification and chromosomal rearrangements, detectable via fluorescence in situ hybridization (FISH) and next-generation sequencing (NGS), are direct indicators of MYC dysregulation. Elevated MYC mRNA levels, as measured by quantitative PCR, show increased transcriptional activity. Moreover, the expression profiles of MYC target genes, particularly LDHA and other cell cycle and metabolic regulators,

provide indirect information on MYC function. Proteomic and metabolic indicators at the protein level, as well as immunohistochemical detection of MYC and its downstream effectors, provide important information on its activity in tumour cells. Metabolic markers, such as altered levels of glutamine, lactate, and other important metabolites, demonstrate MYC-induced metabolic reprogramming.[90] Such alterations can be tracked using improved metabolomic profiling techniques, which improves our capacity to forecast tumor activity and therapy response. Integrating biomarkers into medical practice may assist in guide focused therapies. For example, cancers with high MYC activity may be properly treated with BET inhibitors or drugs that disrupt the MYC-MAX association. Furthermore, patients with metabolic disorders which is affected by malignancy that show MYC-driven glutaminolysis may benefit from glutaminase inhibitors. A multi-biomarker panel could eventually optimize patient categorization, allowing personalized combination medicines that maximize efficacy while minimizing resistance.[91] In a study, the association of E-box with HIF-α and MYC was found to enhance glycolysis which leads to Breast cancer progression. Several proteins are predicted to contain the bHLH domain that can bind with E boxes. These are the facts that could provide the idea for developing therapies and drugs by targeting MYC to give better treatment against Breast Cancer.

Conclusion

Breast cancers with molecular profiles are the most prevalent example and are distinguished by a distinct group of diagnostic and prognostic indicators. Since there are currently no recognized targeted medicines for “breast cancer”, chemotherapy is the major adjuvant and metastatic mode of treatment, even if it is not always diagnosed at a later stage.

Individuals with the metabolic dysregulation mutation are known to have a higher risk of breast cancer. The prevention of Breast Cancer poses significant challenges as current treatment options are limited. However, extensive research is underway to identify "drugable" targets and pathways, as well as explore therapy approaches and utilize advanced processes like developing targeted inhibitors. These efforts are crucial for gaining insights into the aggressive biology of Breast Cancer and developing novel therapeutic strategies that can effectively target the disease. By uncovering key molecular mechanisms and metabolic alterations associated with MYC, researchers strive to enhance patient outcomes by unlocking possibilities to more efficient therapies. Continued, targeted research in this sector will ensure the development of novel approaches in the prevention of Breast Cancer, with the ultimate goal of replacing generic standard-of-care medication with rationally developed treatment.

Acknowledgments

The authors sincerely acknowledge UPES Dehradun for providing support and research facilities.

Conflict of Interest Statement

Authors declare that there is no conflict of interest

Abbreviations

PI3K: Phosphoinositide 3-kinase
RTK: Receptor tyrosine kinase
GLU: Glucose
RIDD: RNA in IRE1-dependent decay
IRE1: Inositol-requiring enzyme1
PERK: Protein kinase R-like endoplasmic reticulum kinase
HIF: Hypoxia Inducible Factor
PKM2: Pyruvate Kinase Type2
LDHA: Lactate Dehydrogenase
UPR: Unfolded Protein Response
DDR: DNA Damage Repair
IERK: Inositol Requiring Enzyme α
ATF6: Activating Transcription Factor 6
TCF: T-cell Factor
STAT3: Signal Transducer and Activation of Transcription

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